

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (original) A method of determining whether a compound enhances formation of a complex between a wild-type p66 subunit polypeptide of HIV-1 reverse transcriptase and a wild-type p51 subunit polypeptide of HIV-1 reverse transcriptase and/or enhances formation of a complex between a p66 subunit having at least one mutation associated with resistance of HIV-1 to at least one nonnucleoside reverse transcriptase inhibitor (NNRTI) and a wild-type p51 subunit of HIV-1 reverse transcriptase, said method comprises:

a) contacting a yeast cell with the compound, which cell comprises (i) a first plasmid which expresses a fusion protein comprising a wild-type p66 subunit polypeptide of HIV-1 reverse transcriptase, (ii) a second plasmid which expresses a fusion protein comprising a wild-type p51 subunit polypeptide of HIV-1 reverse transcriptase, and (iii) a reporter gene which is activated in the presence of a complex between the wild-type p66 subunit polypeptide and the wild-type p51 subunit polypeptide, and determining the level of activity of the reporter gene in the cell in the presence of the compound; and

b) comparing the level of activity of the reporter gene determined in step (a) with a level of activity of the reporter gene determined in the absence of the compound, wherein an increased level of activity of the reporter gene determined in step (a) indicates that the compound is an activator of the formation of the complex between the wild-type p51 subunit polypeptide of HIV-1 reverse transcriptase and the wild-type p66 subunit polypeptide of HIV-1 reverse transcriptase; and

c) contacting a yeast cell with the compound, which cell comprises (i) a third plasmid which expresses a fusion protein comprising a p66 subunit polypeptide of HIV-1 reverse transcriptase having at least one mutation associated with resistance of HIV-1 to at least one NNRTI, (ii) a second plasmid which expresses a fusion protein comprising a wild-type p51 subunit polypeptide of HIV-1 reverse transcriptase, and (iii) a reporter gene which is activated in the presence of a complex between the p66 subunit polypeptide having at least one mutation and the wild-type p51 subunit polypeptide, and determining the level of activity of the reporter gene in the cell in the presence of the compound; and

d) comparing the level of activity of the reporter gene determined in step (c) with a level of activity of the reporter gene determined in the absence of the compound, wherein an increased level of activity of the reporter gene determined in step (c) indicates that the compound is an activator of the formation of the complex between the wild-type p51 subunit polypeptide of HIV-1 reverse transcriptase and the p66 subunit polypeptide of HIV-1 reverse transcriptase having at least one mutation associated with resistance of HIV-1 to at least one NNRTI.

2. (original) The method according to claim 1, wherein the mutation is associated with at least 5-fold or greater resistance of HIV-1 to at least one NNRTI.

3. (original) The method according to claim 1, wherein the mutation is associated with at least a ten-fold or greater resistance of HIV-1 to at least one NNRTI.

4. (original) The method according to claim 1, wherein the p66 subunit polypeptide has one mutation, the mutation is associated with an increase in resistance of HIV-1 to at least one NNRTI.

5. (original) The method according to claim 1, wherein the p66 subunit polypeptide has two mutations, each mutation is associated with an increase in resistance of HIV-1 to at least one NNRTI.

6. (original) The method according to claim 1, wherein the p66 subunit polypeptide has three mutations, each mutation is associated with an increase in resistance of HIV-1 to at least one NNRTI.

7. (original) The method according to claim 1, wherein the p66 subunit polypeptide has four mutations, each mutation is associated with an increase in resistance of HIV-1 to at least one NNRTI.

8. (original) The method according to claim 1, wherein the p66 subunit polypeptide has five mutations, each mutation is associated with an increase in resistance of HIV-1 to at least one NNRTI.

9. (original) The method according to claim 1, wherein the p66 subunit polypeptide mutation is F227L, G190A, G190E, G190S, K101E, K103N, K238T, L100I, P225H, V106A, V106I, V108I, Y181C, Y188H, Y188L, or combinations thereof.

10. (original) The method according to claim 9, wherein the p66 subunit polypeptide mutation is L100I and K103N.

11. (currently amended) The method according to claim 9, wherein the p66 subunit polypeptide mutation is selected from the group consisting of: K103N and Y181C; K101E and K103N; K103N and Y188H; V106I and Y188L; K103N and P225H; and K103N and V108I.

12. (currently amended) The method according claim 9, wherein a first mutation is K103N or Y188L and a second mutation is selected from the group consisting of: V106I, V108I, Y181C, Y188H, P225H and F227L.

13. (original) The method according to claim 1, wherein the yeast strain is CTY10-5d having the genotype: MATa ade2 trp1-901 leu2-3 112 his3-200 gal4-gal80-URA3::lexA-lacZ.

14. (withdrawn) A compound determined to be capable of enhancing formation of a complex between a p66 subunit polypeptide of HIV-1 reverse transcriptase having at least one mutation and a wild-type p51 subunit polypeptide of HIV-1 reverse transcriptase by the method of claim 1.

15. (withdrawn) The compound according to claim 14, wherein the compound inhibits HIV-1.

16. (withdrawn) The compound according to claim 14, wherein the enhanced formation of complex formation by the compound is measured by enhancement of the activity of the reporter gene.

17. (withdrawn) The compound according to claim 14, wherein the p66 subunit polypeptide of HIV-1 reverse transcriptase has one mutation, the mutation is associated with an increased resistance of HIV-1 to at least one NNRTI.

18. (withdrawn) The compound according to claim 14, wherein the p66 subunit polypeptide of HIV-1 reverse transcriptase has two mutations, each mutation is associated with an increase in resistance of HIV-1 to at least one NNRTI.

19. (withdrawn) The compound according to claim 14, wherein the p66 subunit polypeptide of HIV-1 reverse transcriptase has three mutations, each mutation is associated with an increase in resistance of HIV-1 to at least one NNRTI.

20. (withdrawn) The compound according to claim 14, wherein the p66 subunit polypeptide of HIV-1 reverse transcriptase has four mutations, each mutation is associated with an increase in resistance of HIV-1 to at least one NNRTI.

21. (withdrawn) The compound according to claim 14, wherein the p66 subunit polypeptide of HIV-1 reverse transcriptase has five mutations, each mutation is associated with an increase in resistance of HIV-1 to at least one NNRTI.

22. (withdrawn) The compound according to claim 14, wherein the mutation is F227L, G190A, G190E, G190S, K101E, K103N, K238T, L100I, P225H, V106A, V106I, V108I, Y181C, Y188H, Y188L, or combinations thereof.

23. (withdrawn) The compound according to claim 22, wherein the mutation is selected from the group consisting of, L100I and K103N; Y181C and K103N; K101E and K103N; K103N and Y188H; V106I and Y188L; 103N and P225H, and K103N and V108I.

24. (withdrawn) The compound according to claim 22, wherein a first mutation is K103N or Y188L and a second mutation is selected from the group consisting of V106I, V108I, Y188H, P225H, and F227L.

25. (withdrawn) The compound according to claim 14, wherein an enhancement of formation of a complex between a p66 subunit polypeptide of HIV-1 reverse transcriptase having at least one mutation associated with an increased resistance of HIV-1 to at least one NNRTI and a wild-type p51 subunit polypeptide of HIV-1 reverse transcriptase is

comparable to an enhancement of formation of a complex between a wild-type p66 subunit polypeptide of HIV-1 reverse transcriptase and a wild-type p51 subunit polypeptide of reverse transcriptase at a given compound concentration.

26. (withdrawn) The compound according to claim 25, wherein the enhancement obtained using the p66 subunit having at least one mutation associated with an increase in resistance of HIV-1 to at least one NNRTI and the enhancement obtained using wild-type p66 are within plus-or-minus 15%.

27. (withdrawn) The compound according to claim 25, wherein the formation of complex by the compound using mutant p66 or wild-type p66 is greater than formation of complex by a known NNRTI using mutant p66 or wild-type at a given concentration, that concentration being in a linear range of enhancement effects for both the compound and the known NNRTI.

28. (withdrawn) The compound according to claim 14, which has little or no enhancement of formation of complex between the wild-type p66 subunit polypeptide and the wild-type p51 subunit polypeptide.

29. (withdrawn) The compound according to claim 14, wherein the enhancement of formation of complex between the p66 subunit having at least one mutation associated with an increase in resistance of HIV-1 to at least one NNRTI and wild-type p51 subunit is greater than the enhancement of formation of complex between wild-type p66 subunit and wild-type p51 subunit.

30. (withdrawn) The compound according to claim 29, wherein the enhancement of complex formation between the p66 subunit having at least one mutation

associated with an increase in resistance of HIV-1 to at least one NNRTI and wild-type p51 subunit is greater than 25% of the enhancement of complex formation between wild-type p66 subunit and wild-type p51 subunit.

31. (withdrawn) The compound according to claim 29, wherein the enhancement of complex formation between the p66 subunit having at least one mutation associated with an increase in resistance of HIV-1 to at least one NNRTI and wild-type p55 subunit is at least 30% of the enhancement of complex formation between wild-type p66 subunit and wild-type p51 subunit.

32. (withdrawn) The compound according to claim 29, wherein the enhancement of complex formation between the p66 subunit having at least one mutation associated with an increase in resistance of HIV-1 to at least one NNRTI and wild-type p51 subunit is at least 50% of the enhancement of complex formation between the wild-type p66 subunit and wild-type p51 subunit.

33. (withdrawn) The compound according to claim 29, wherein the enhancement of complex formation between the p66 subunit having at least one mutation associated with an increase in resistance of HIV-1 to at least one NNRTI and wild-type p51 subunit is at least 75% of the enhancement of complex formation between the wild-type p66 subunit and wild-type p51 subunit.

34. (withdrawn) The compound according to claim 29, wherein the enhancement of complex formation between p66 subunit having at least one mutation associated with an increase in resistance of HIV-1 to at least one NNRTI and wild-type p51 subunit is about

30% to about 100% of the enhancement of complex formation between wild-type p66 subunit and wild-type p51 subunit.

35. (withdrawn) The compound according to claim 29, wherein the enhancement of complex formation between p66 subunit having at least one mutation associated with an increase in resistance of HIV-1 to at least one NNRTI and wild-type p51 subunit is about 40% to about 100% of the enhancement of complex formation between wild-type p66 subunit and wild-type p51 subunit.

36. (withdrawn) The compound according to claim 29, wherein the enhancement of complex formation between p66 subunit having at least one mutation associated with an increase in resistance of HIV-1 to at least one NNRTI and wild-type p51 subunit is about 50% to about 100% of the enhancement of complex formation between wild-type p66 subunit and wild-type p51 subunit.

37. (withdrawn) The compound according to claim 29, wherein the enhancement of complex formation between p66 subunit having at least one mutation associated with an increase in resistance of HIV-1 to at least one NNRTI and wild-type p51 subunit is about 100% to about 500% of the enhancement of complex formation between wild-type p66 subunit and wild-type p51 subunit.

38. (withdrawn) The compound according to claim 29, wherein the enhancement of complex formation between p66 subunit having at least one mutation associated with an increase in of HIV-1 to at least one NNRTI and wild-type p51 is about 150% to about 1000% of the enhancement of complex formation between wild-type p66 subunit and wild-type p51 subunit.

39. (withdrawn) The compound according to claim 29, wherein the enhancement of complex formation between p66 subunit having at least one mutation associated with an increase in resistance of HIV-1 to at least one NNRTI and wild-type p51 subunit is about 200% to about 1000% of the enhancement of complex formation between wild-type p66 subunit and wild-type p51 subunit.

40. (withdrawn) The compound according to claim 29, wherein the enhancement of complex formation between p66 subunit having at least one mutation associated with an increase in resistance of HIV-1 to at least one NNRTI and wild-type p51 subunit is about 500% to about 1000% of the enhancement of complex formation between wild-type p66 subunit and wild-type p51 subunit.

41. (withdrawn) The compound according to claim 29, wherein the p66 subunit has at least one mutation and the enhancement of complex formation between the p66 subunit having the mutation and the wild-type p51 subunit is higher than the enhancement of complex formation in the presence of a known NNRTI at a given concentration, that concentration being in a linear range of enhancement for both the compound and the known NNRTI.

42. (withdrawn) The compound according to claim 29, wherein the p66 subunit has at least one mutation and the enhancement of complex formation between the p66 subunit having the mutation and the wild-type p51 subunit is higher than the enhancement of complex formation in the presence of (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one (efavirenz) at a given concentration, that concentration being in a linear range of enhancement for both the compound and efavirenz.

43. (withdrawn) The compound according to claim 42, wherein the enhancement of complex formation is at least 20% higher than the enhancement in complex formation in the presence of efavirenz at a given concentration, that concentration being in a linear range of enhancement for both the compound and efavirenz.

44. (withdrawn) The compound according to claim 42, wherein the enhancement of complex formation is at least 25% higher than the enhancement of complex formation in the presence of efavirenz at a given concentration, that concentration being in a linear range of enhancement for both the compound and efavirenz.

45. (withdrawn) The compound according to claim 42, wherein the enhancement of complex formation is at least 30% higher than the enhancement of complex formation in the presence of efavirenz at a given concentration, that concentration being in a linear range of enhancement for both the compound and efavirenz.

46. (withdrawn) The compound according to claim 42, wherein the enhancement of complex formation is at least 50% higher than the enhancement of complex formation in the presence of efavirenz at a given concentration, that concentration being in a linear range of enhancement for both the compound and efavirenz.

47. (withdrawn) The compound according to claim 42, wherein the enhancement of complex formation is about 50% to about 1000 % higher than the enhancement of complex formation in the presence of efavirenz at a given concentration, that concentration being in a linear range of enhancement for both the compound and efavirenz.

48. (withdrawn) The compound according to claim 42, wherein the enhancement of complex formation is about 100% to about 1000% higher than the enhancement

of complex formation in the presence of efavirenz at a given concentration, that concentration being in a linear range of enhancement for both the compound and efavirenz.

49. (withdrawn) The compound according to claim 42, wherein the enhancement of complex formation is about 150% to about 1000 % higher than the enhancement of complex formation in the presence of efavirenz at a given concentration, that concentration being in a linear range of enhancement for both the compound and efavirenz.

50. (withdrawn) The compound according to claim 42, wherein the enhancement of complex formation is about 200% to about 1000 % higher than the enhancement of complex formation in the presence of efavirenz at a given concentration, that concentration being in a linear range of enhancement for both the compound and efavirenz.

51. (withdrawn) The compound according to claim 42, wherein the enhancement of complex formation is about 500% to about 1000% higher than the enhancement of complex formation in the presence of efavirenz at a given concentration, that concentration being in a linear range of enhancement for both the compound and efavirenz.

52. (withdrawn) The compound of claim 14, wherein the compound is a nonnucleoside reverse transcriptase inhibitor.

53. (withdrawn) The compound according to claim 14, wherein the compound is capable of inhibiting the growth of HIV-1.

54. (withdrawn) The compound according to claim 53, wherein the HIV-1 is resistant to at least one NNRTI.

55. (withdrawn) The compound according to claim 53, wherein the HIV-1 has at least one mutation in reverse transcriptase, said mutation is associated with resistance to at least one NNRTI.

56. (withdrawn) The compound according to claim 54 or 55, wherein the NNRTI is known.

57. (withdrawn) The compound of claim 14, wherein the compound is not efavirenz, N-(4-chloro-3-(3-methyl-2-butenyloxy)phenyl)-2-methyl-3-furancarbothioamide (UC-781), nevirapine, delavirdine, SJ-3366, MKC-442, GW420867x or (S)-4-isopropoxycarbonyl-6-methoxy-3-(methylthiomethyl)-3,4-dihydroquinoxaline-2(1H)-thione (HBY 097).

58. (withdrawn) The compound according to claim 14, wherein the compound is a derivative of a compound selected from the group consisting of efavirenz, UC-781, HBY 097, nevirapine, delavirdine, SJ-3366, MKC-442, GW420867x, and HI-443.

59. (withdrawn) The compound according to claim 14, wherein the compound acts at a location on HIV-1 reverse transcriptase distinct from a nonnucleoside reverse transcriptase binding pocket.

60. (withdrawn) A compound capable of inhibiting HIV-1, said inhibition characterized by enhancing formation of a complex between a p66 subunit polypeptide and a p51 subunit polypeptide of reverse transcriptase of the HIV-1, wherein the HIV-1 is wild-type or the HIV-1 has at least one mutation associated with resistance to at least one NNRTI.

61. (withdrawn) The compound according to claim 60, wherein the mutation is in the p66 subunit and the p51 subunit of reverse transcriptase.

62. (withdrawn) The compound according to claim 60, wherein the mutation is F227L, G190A, G190E, G190S, K101E, K103N, K238T, L100I, P225H, V106A, V106I, V108I, Y181C, Y188H, Y188L, or combinations thereof.

63. (withdrawn) The compound according to claim 60, wherein the mutation is selected from the group consisting of K103N, and Y181C; K101E and K103N; K103N and Y188H; V106I and Y188L; K103N and P225H; and K103N and V108I.

64. (withdrawn) The compound according to claim 60, wherein a first mutation is K103N or Y188L and a second mutation is selected from the group consisting of V106I, V108I, Y181C, Y188H, P225H and F227L.

65. (withdrawn) The compound according to claim 60, wherein the compound is derived from a combinatorial chemical library.

66. (withdrawn) The compound according to claim 60, wherein the compound is derived from a synthetic chemical library.

67. (withdrawn) The compound according to claim 60, wherein the compound is a nonpeptidyl agent having a molecular weight of less than 1000 daltons.

68. (withdrawn) The compound according to claim 60, wherein the compound is an NNRTI.

69. (withdrawn) The compound according to claim 68, wherein the compound is a derivative of efavirenz, UC-781, HBY 097, nevirapine, delavirdine, SJ-3366, MKC-442, GW420867x or HI-443.

70. (withdrawn) The compound according to claim 60, wherein the compound has an IC₅₀ value against growth of HIV-1 of less than one nanomolar.

71. (withdrawn) The compound according to claim 60, wherein the compound has an IC_{50} value against the growth of HIV-1 in a range of about 0.01 nM to about 1.0 nM.

72. (withdrawn) A composition comprising at least one compound according to any one of claims 16 or 60 and a pharmaceutically acceptable carrier.

73. (withdrawn) The composition according to claim 72, further comprising at least one known NNRTI, a nucleoside reverse transcriptase inhibitor, an HIV-1 protease inhibitor, or combinations thereof.

74. (withdrawn) The composition according to claim 73, wherein the known NNRTI is selected from the group consisting of efavirenz, UC-781, HBY 097, nevirapine, delavirdine, SJ-3366, MKC-442, GW420867x, and HI-443 and combinations thereof.

75. (withdrawn) The composition according to claim 73, wherein the nucleoside reverse transcriptase inhibitor is selected from the group consisting of abacavir, lamivudine, zidovudine, stavudine, zalcitabine, didanosine, and combinations thereof.

76. (withdrawn) The compositions according to claim 73, wherein the HIV-1 protease inhibitor is selected from the group consisting of lopinavir, saquinavir, nelfinavir, indinavir, amprenavir, ritonavir, and combinations thereof.

77. (withdrawn) A method of enhancing formation of a complex between a p66 subunit polypeptide of HIV-1 reverse transcriptase and a p51 subunit polypeptide of reverse transcriptase, which comprises contacting the subunits with an effective amount of at least one compound according to claim 14, so to thereby enhance formation of a complex between the p66 subunit polypeptide and the p51 subunit polypeptide of HIV-1 reverse transcriptase.

78. (withdrawn) The method according to claim 77, wherein the HIV-1 reverse transcriptase has at least one mutation associated with resistance to at least one NNRTI.

79. (withdrawn) The method according to claim 77, wherein the HIV-1 reverse transcriptase is present in a subject and the contacting is effected by administering the compound to the subject.

80. (withdrawn) The method of claim 79, wherein the compound is administered orally, intravenously, subcutaneously, intramuscularly, topically, or by liposome-mediated delivery.

81. (withdrawn) The method according to claim 79, wherein the subject is a human, a non-human primate, an equine, an opine, an avian, a bovine, a porcine, a canine, a feline, or a mouse.

82. (withdrawn) The method according to claim 79, wherein the effective amount of the compound is between about 1mg and about 50mg per kg body weight of the subject.

83. (withdrawn) The method according to claim 79, wherein the effective amount of the compound is between about 2mg and about 40 mg per kg body weight of the subject.

84. (withdrawn) The method according to claim 79, wherein the effective amount of the compound is between about 3mg and about 30 mg per kg body weight of the subject.

85. (withdrawn) The method according to claim 79, wherein the effective amount of the compound is about 4mg and about 20mg per kg body weight of the subject.

86. (withdrawn) The method according to claim 79, wherein the effective amount of the compound is between about 5mg and about 10mg per kg body weight of the subject.

87. (withdrawn) The method according to claim 79, wherein the compound is administered at least once per day.

88. (withdrawn) The method according to claim 79, wherein the compound is administered daily.

89. (withdrawn) The method according to claim 79, wherein the compound is administered every other day.

90. (withdrawn) The method according to claim 79, wherein the compound is administered every 6 to 8 days.

91. (withdrawn) The method according to claim 79, wherein the compound is administered weekly.

92. (withdrawn) A method of inhibiting the growth of HIV-1 comprising administration of at least one compound according to claim 14 or 60, in an amount effective to inhibit HIV-1.

93. (withdrawn) The method according to claim 92, wherein the HIV-1 has at least one mutation in subunit polypeptides of reverse transcriptase.

94. (withdrawn) The method according to claim 93, wherein a p51 subunit polypeptide of reverse transcriptase of the HIV-1 has a mutation corresponding to a mutation in a p66 subunit polypeptide.

95. (withdrawn) The method according to claim 92, wherein the HIV-1 is resistant to at least one NNRTI.

96. (withdrawn) The method according to claim 92, further comprising the administration of at least one known NNRTI, a nucleoside reverse transcriptase inhibitor, an HIV-1 protease inhibitor, or combinations thereof.

97. (withdrawn) A method of treating infection by HIV-1 or for treating AIDS in a subject comprising administration of an amount of at least one compound according to claim 14 or 60, said amount effective to treat the infection or AIDS.

98. (withdrawn) The method according to claim 97, wherein the HIV-1 in the subject has at least one mutation in a reverse transcriptase gene.

99. (withdrawn) The method according to claim 97, wherein the HIV-1 viral load of the subject has increased with conventional NNRTI therapy.

100. (original) A method of making a pharmaceutical composition which comprises:

- a) determining whether a compound enhances formation of complex by the method of claim 1;
- b) recovering the compound; and
- c) admixing the compound with a pharmaceutically acceptable carrier.